

Inflammatory Aortic Aneurysms

A Clinical Review with New Perspectives in Pathogenesis

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Objective

The authors present a review of abdominal aortic aneurysms (AAAs) and to examine the literature on the diagnosis, operative management, and long-term survival of patients with inflammatory AAAs. Furthermore, to review current theories on the cause of inflammatory AAAs and present recent studies that provoke new thought on the cause of these aneurysms.

Background Data

Inflammatory AAAs represent 3% to 10% of all AAAs and present the surgical team with a unique challenge. Progress has occurred in the technical approach to these aneurysms, and operative morbidity and mortality have been reduced. However, the pathogenesis remains an enigma. Recent studies raise questions regarding the influence of tobacco and genetic factors that accentuate an antigen-driven inflammatory response.

Methods

The authors conduct a review of the literature on both noninflammatory and inflammatory AAAs.

Results

Review of the literature of inflammatory AAAs reveals advancement in the definition, diagnosis, management, and long-term survival of patients with inflammatory AAAs. This review found an evolution in thought regarding the cause of inflammatory AAAs. In contrast to initial reports describing a distinct clinical entity, recent evidence suggests that inflammatory AAAs arise from the same causal stimulus responsible for noninflammatory AAAs. Finally, recent studies show an influence of tobacco and genetic factors on the pathogenesis.

Conclusions

The literature supports the theory that inflammatory AAAs arise from the same or similar antigenic stimulus which is responsible for the noninflammatory AAA. Genetic and chemical factors such as tobacco use predispose certain persons to the development of noninflammatory AAAs and others to develop the extreme end of an inflammatory spectrum, the inflammatory AAA. Furthermore, inflammatory AAAs can be managed with the same operative morbidity, mortality, and long-term survival as noninflammatory AAAs.

Renewed interest in the vascular entity known as the inflammatory abdominal aortic aneurysm (AAA) is leading to a better understanding of all aortic aneurysms.¹⁻⁹ In this article, we will link the incidence, clinical presentation, and surgical management with new concepts in the pathogenesis of inflammatory AAAs. We present evidence that the inflammatory AAA may not be a distinct clinical and etiological entity but the extreme end of an antigen-driven inflammatory spectrum responsible also for the noninflammatory AAA.

In 1952, Charles Dubost became the first surgeon to report the repair of an abdominal aortic aneurysm with a cadaveric homograft.¹⁰ In the 1960s, De Bakey in Houston, Linton in Boston, and Cannon in Los Angeles established surgical repair of the AAA as the standard of care. They established that mortality rates associated with surgical repair were lower than nonoperative observation.¹¹⁻¹³ In De Bakey's review of 1449 patients undergoing repair of AAAs, he did not mention inflammatory abdominal aneurysms.¹¹ Although a few case reports described obstructive uropathy from perianeurysmal fibrosis associated with some aneurysms,¹⁴⁻¹⁸ the term inflammatory aneurysm was not used.

In 1972, Walker et al. were the first to use the term inflammatory abdominal aortic aneurysm.¹ They described a distinct form of aneurysm characterized by "an unusually thick wall surrounded by extensive fibrous adhesions involving adjoining tissues and structures making the operative procedure much more difficult." These extraordinary clinicopathologic findings were found in 10% of the aneurysms that they described. At that time, the view of abdominal aortic aneurysms changed, and a separate clinical entity, the inflammatory aneurysm, was recognized.

DEFINITION

Surgeons agree that the triad of thickened aneurysm wall, extensive perianeurysmal and retroperitoneal fibrosis, and dense adhesions of adjacent abdominal organs defines the inflammatory AAA (Fig. 1).^{2,3,7} These criteria are identical to the original descriptions by Walker who described a "thick, firm, smooth wall of the aneurysm which is shiny white in appearance." He also noted the "dense fibrosis which extends to involve adjacent structures."¹ Undoubtedly this is the same process described by James and DeWeerd in their original descriptions of these aneurysms in 1935 and 1955 respectively.^{14,15}

INCIDENCE

Inflammatory AAAs represent 3% to 10% of all abdominal aortic aneurysms^{1-9,19} and have a distinct ten-

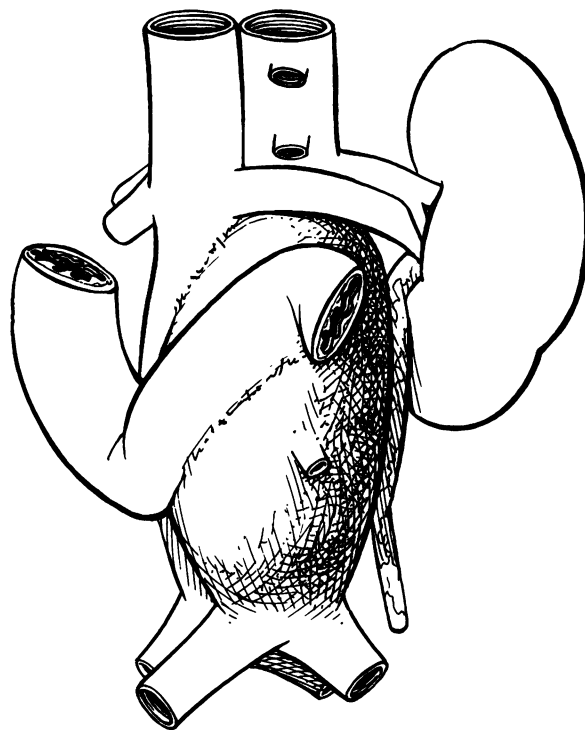


Figure 1. Inflammatory, infrarenal abdominal aortic aneurysm with adherent duodenum and ureters.

dency to occur in men. The male to female ratio varies from 30:1 to 6:1 depending on the series.^{2,7,9,20} The mean age of patients in Walker's original study was 62 years,¹ and this age range has been confirmed with later studies demonstrating mean ages of occurrence from 62 to 68 years.^{2-9,19,20} Interestingly, this age is 5 to 10 years younger than the mean age of patients with noninflammatory AAAs.

The percentage of patients with inflammatory AAAs who smoke is high, ranging from 100% of patients in two separate studies by Crawford and Goldstone^{3,5} to 77% patients in a study by Sterpetti et al.⁷ Furthermore, a recent case-control study by Nitecki et al. showed that a significantly higher percentage of patients with inflammatory aneurysms were current smokers compared to patients with noninflammatory aneurysms.¹⁹ Interestingly, Walker's initial report in 1972 did not mention smoking.¹

A familial tendency to the development of aneurysms exists in 6.1% to 15.1% of noninflammatory AAAs.²¹⁻²⁴ Few series of inflammatory AAAs mention family history. Pennell et al. found a family history of aneurysms in 7.6% of patients with inflammatory aneurysms.² Significantly, the case-control study by Nitecki et al. showed for the first time that a higher percentage of patients with inflammatory AAAs had a positive family history (17%) when compared with patients with noninflammatory aneurysms (1.7%).¹⁹ These clinical observations of familial tendencies in both inflammatory and noninflammatory

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AAAs provide indirect evidence of a genetic predisposition to the development of this disease.

PRESENTATION

Symptoms

The symptomatic nature of the inflammatory AAA has been well characterized. As Nitecki et al. reports, the triad of abdominal or back pain, weight loss, and an elevated erythrocyte sedimentation rate in patients with abdominal aortic aneurysms is highly suggestive of an inflammatory aneurysm.¹⁹ Only 3 of the 19 patients with inflammatory abdominal aneurysms described by Walker et al. were asymptomatic.¹ Goldstone et al.³ and Crawford et al.,⁵ report 80% of patients with inflammatory AAAs have symptoms of abdominal, flank, or back pain. In similar studies, symptoms referable to the inflammatory AAA are reported to exist in 65% to 90% of patients.^{2,4,6,7} This rate of presenting symptoms is significantly higher than patients with noninflammatory AAAs, of which only 8% to 18% of patients have symptoms.^{7,19} Weight loss and anorexia occur in at least 20% to 41% of patients with inflammatory AAAs and can be significant (mean, 25 pounds).^{6,19}

Physical Findings

In Walker's study, 26% of patients with an inflammatory AAA had a pulsatile abdominal mass on examination.¹ More recent studies have found that a tender, pulsatile abdominal mass is present in 15% to 30% of such patients.^{2,6,8}

An abnormally elevated erythrocyte sedimentation rate signifying an increase in acute phase reactants is the most frequent laboratory abnormality. Walker reported this elevation of erythrocyte sedimentation rate in his original description of inflammatory aneurysms,¹ and subsequent reports confirm his observations. An elevated erythrocyte sedimentation rate is reported in 40% to 88% of patients with inflammatory AAAs, a significantly greater percentage of patients than with noninflammatory AAAs.^{2,4,9,19} Reports of fever and leukocytosis in patients with inflammatory aneurysms exist;^{4,19} however, these findings seem to be more variable. In fact, some investigators report normal leukocyte counts and no fever in patients with inflammatory AAAs.⁵

Associated Comorbidities

Arterial hypertension and arterial occlusive disease are frequent comorbidities associated with both inflammatory and noninflammatory AAAs. Arterial hypertension affects 34% to 69% of patients with inflammatory AAAs, and arterial occlusive disease is present in 10% to 47% of

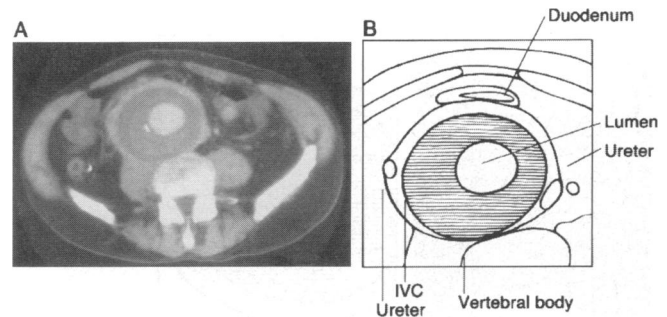


Figure 2. (A) Abdominal CT scan showing an inflammatory abdominal aortic aneurysm with adherent duodenum and ureters. (B) Note the thickened aortic wall and thrombus within the lumen of the aneurysm.

patients.^{2,4,7,19} Not surprisingly, the percentage of patients with these associated findings does not vary significantly from patients with noninflammatory AAAs.

Associated diabetes mellitus is present in 3% to 13% of patients with inflammatory AAAs.^{2,4,7,19} There seems to be no significant difference in the prevalence of diabetes in patients with inflammatory versus noninflammatory AAAs.

Coronary artery disease is a common comorbidity in patients with both inflammatory and noninflammatory AAAs. Associated coronary artery disease affects 33% to 55% of patients with inflammatory AAAs.^{2,3,19} In the case control study by Nitecki et al., the same percentage of inflammatory and noninflammatory aneurysm patients (55%) had associated coronary artery disease.¹⁹

Entrapment of the ureters in the retroperitoneal fibrotic process is common and occurs in varying degrees. Stella et al. reported involvement of the ureters in the periaortic mass in 53% of patients with inflammatory aneurysms as documented by computed tomography (CT) scan.⁹ Obstructive uropathy, which was described in the earliest accounts of inflammatory aneurysms,^{14–18} afflicts 10% to 21% of patients with inflammatory AAAs.^{2–4,7,8} Similarly, chronic renal dysfunction is present in 18% to 21% of such patients.^{9,19}

Diagnostic Tests

Preoperative diagnosis of inflammatory AAAs is the exception and occurs in only 13% to 33% of patients.^{2,7,8,20} Although its sensitivity is not absolute, the abdominal CT scan (Fig. 2) is the most reliable radiographic study to detect aneurysmal wall thickening and perianeurysmal soft tissue changes suggestive of an inflammatory AAA.^{2,3,20,25} Most studies report retrospective readings after the inflammatory aneurysm has been discovered operatively. However, a recent Mayo Clinic study found good sensitivity for detecting an inflammatory AAA by CT scan or ultrasound, 90% versus 60%, respectively.¹⁹ Clearly, evidence of inflammatory aneurysms is present

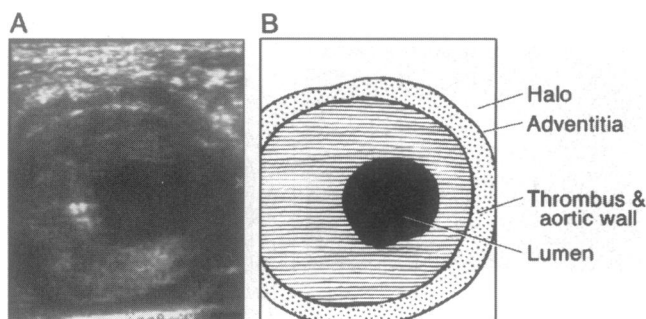


Figure 3. (A) Abdominal ultrasound of an inflammatory abdominal aortic aneurysm. (B) Note the "inflammatory halo" surrounding the aneurysm and its thickened wall.

on the majority of abdominal CT scans. The accuracy in making the diagnosis depends on the clinician's and radiologist's awareness and knowledge of this disease phenomenon.

High-resolution ultrasound can also detect the inflammatory AAA wall in many patients. The distinct finding is a sonolucent halo described originally by Henry et al.²⁶ and Bundy and Ritchie²⁷ (Fig. 3). However, the inflammatory halo may not be present on all ultrasound studies. The accuracy of ultrasound in identifying the inflammatory component to an AAA is reported to be less than that of abdominal CT scan.^{2,19} Pennell et al. demonstrated the prospective ability of ultrasound to diagnose an inflammatory aneurysm in only 13.5% of patients.² Retrospectively, these ultrasound studies were reinterpreted as having findings suggestive of an inflammatory AAA in 60% of patients.

Preoperative excretory pyelography shows findings suggestive of an inflammatory aneurysm in 25% to 30% of patients.^{2,3,7} Similar to their findings with abdominal CT scan, Sterpetti et al. found that retrospective review of the pyelography revealed findings suggestive of an inflammatory AAA in all patients.⁷ These findings included varying degrees of ureteral obstruction or deviation from the extensive retroperitoneal inflammation and fibrosis. Intravenous pyelography and an abdominal CT scan seem to be the best preoperative combination to define the course of the ureters.

Recent reports have used the technique of gadolinium-enhanced magnetic resonance imaging to diagnose inflammatory AAAs.^{28,29} They emphasize the excellent delineation of the periaortic inflammatory mantle and aortic lumen. Neither the clinical nor the cost benefits of this technique compared with the abdominal CT scan or ultrasound have been established.

Although indications for angiography in patients with AAAs exist, the literature has shown no benefit in the detection of associated inflammation with this diagnostic modality.

THERAPY

Although the rate of rupture of inflammatory AAAs is generally accepted to be lower than that of the noninflammatory aneurysm,^{5,30,31} their natural history seems to involve enlargement and rupture.^{1,2,5,7,32} Reports of nonoperative management with corticosteroids include only case reports or small series of patients deemed inoperable at the time of laparotomy.³³⁻³⁵ In one such study by Baskerville et al., five patients were observed while on oral corticosteroids.³⁵ During the 18-month period of surveillance by abdominal CT scans, one patient underwent emergent operation for signs of rupture. No follow-up longer than 18 months is offered in the remaining patients. No controlled clinical trials have evaluated the long-term efficacy of steroids for inflammatory AAAs.

Most authors agree that corticosteroids do not alter the long-term development of inflammatory aneurysms and that operative repair of the aneurysm is the treatment of choice.^{2,3,7,19,20} If corticosteroids reduce the periaortic fibrous reaction, many investigators suggest that the tendency to rupture may be increased. Furthermore, with operative techniques to minimize dissection of the duodenum and ureters, the operative mortality rate for repair of the inflammatory abdominal aneurysm^{2,3,7,19} approaches that reported in a large review of noninflammatory AAAs, 1.4% to 6.5%.³⁶

OPERATIVE FINDINGS

Findings at operation are characterized by the thickened aortic wall, from 0.5 to 3.0 cm, and a shiny, white periaortic and retroperitoneal inflammatory reaction. Most commonly, the inflammatory adhesions involve the duodenum (range, 97–100%), inferior vena cava (range, 63–70%), and the left renal vein (range, 48–51%). Other structures less frequently involved in the inflammatory process are the ureters (range, 20–44%), small bowel (20%), and sigmoid colon (range, 5–20%)^{2,5,7,19} (Fig. 4).

At the time of surgical repair, the size of inflammatory AAAs is generally larger than noninflammatory aneurysms. Goldstone et al. reported a mean size of inflammatory aneurysms as 10.2 cm *versus* 7.8 cm for noninflammatory aneurysms.⁵ In separate comparative studies, Sterpetti et al. and Nitecki et al. also reported that inflammatory aneurysms are larger in transverse diameter than noninflammatory aneurysms.^{7,19}

Other arterial aneurysms found at the time of operation are common but are not usually inflammatory in gross appearance. Pennell et al. reported that aneurysmal disease other than the infrarenal aorta occurred most commonly in the iliac arteries (43%), followed by the thoracoabdominal aorta (13%), femoral (13%), and popliteal (8%) arteries. Fifty percent of the patients with inflammatory AAAs had no associated aneurysmal disease.²

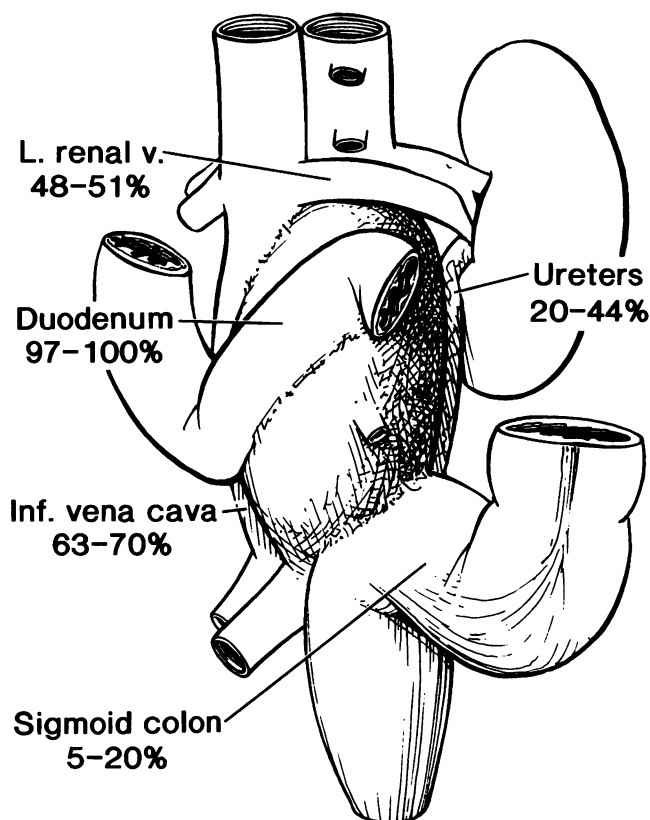


Figure 4. Inflammatory abdominal aortic aneurysm with associated adherent viscera and the frequency with which each structure is adherent to the aneurysm.

In early experiences with inflammatory AAAs, surgeons attempted extensive adhesiolysis of perianeurysmal structures. These attempts were complicated by enterotomies, especially of the duodenum, and injuries to the ureters and the vena cava, substantially affecting operative mortality. In 1978, Goldstone et al. described the importance of a modified operative approach to the inflammatory AAA. He emphasized the hazards of attempted mobilization of the duodenum from the anterior wall of the aneurysm and advised obtaining proximal and distal control of the aneurysm “with as little dissection as possible”⁵ (Fig. 5).

In a 1985 review of patients with inflammatory aneurysms, Crawford also advised against dissection of surrounding structures. In addition, he advocated aortic cross clamping at the diaphragm until the proximal anastomosis is completed.³ With this technique of limited dissection, he described operative mortality rates of 3% to 4%, matching those of noninflammatory aneurysms. Pennell et al reviewed three decades of inflammatory AAA repair, the 1950s through the 1980s, and showed that the operative mortality rate improved in each decade.² From 1955 to 1964, the operative mortality rate was 12.5%; from 1965 to 1974, 8.3%; and from 1975 to 1984, 4.2%. Similar improvements were found in long-term survival rates

of patients with inflammatory aneurysms. With these modified operative techniques, this study showed that both operative mortality and late survival improved and were comparable to patients with noninflammatory aneurysms (Fig. 6).

Controversy exists regarding ureterolysis during repair of inflammatory AAAs. Nearly 50% of abdominal CT scans show ureteral involvement in the perianeurysmal inflammation and up to 20% of patients present with signs and symptoms of ureteral obstruction. Concerns for persistent or recurrent obstruction exist.

The incidence of recurrent ureteral obstruction after repair of the inflammatory AAA is extremely rare and has been reported only once by Boontje et al.⁸ In his study he reports uncomplicated ureterolysis in 12 of the 45 patients undergoing aneurysm repair. One 45-year-old patient who had undergone ureterolysis at the time of aneurysm repair presented 10 months postoperatively with recurrent ureteral obstruction requiring another operation. Boontje and others advocate routine ureterolysis at the

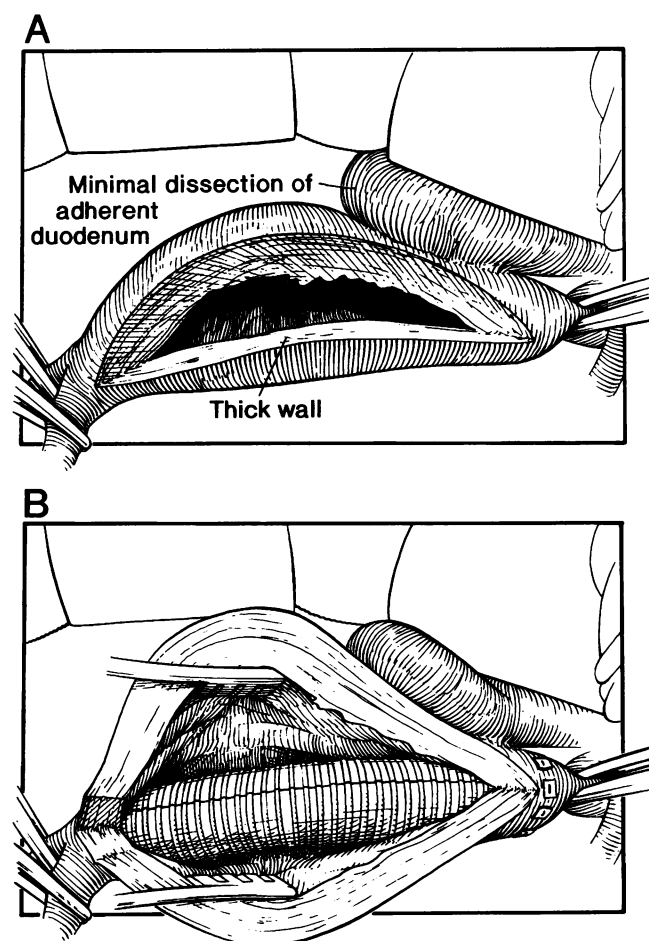


Figure 5. (A) Repair of an inflammatory abdominal aortic aneurysm. Note minimal dissection of duodenum from the thickened aneurysm wall and infrarenal cross-clamp on the aorta. (B) Insertion of tube graft into an inflammatory abdominal aortic aneurysm during repair.

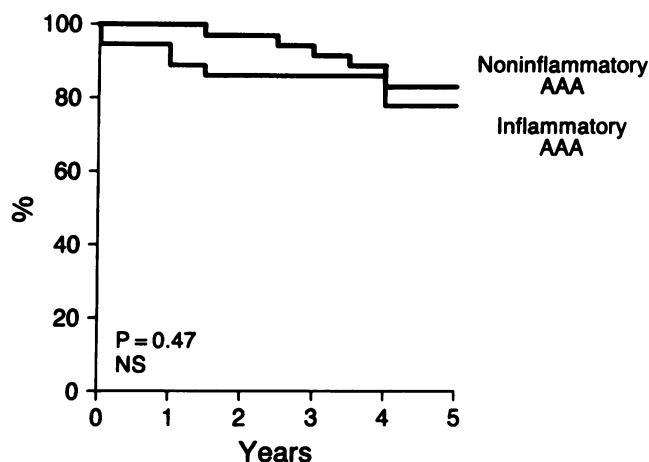


Figure 6. Five-year survival rates for patients undergoing operative repair of inflammatory vs. noninflammatory abdominal aortic aneurysms.

time of inflammatory aneurysm repair for obstruction and in select cases where no obstruction exists.^{8,37,38}

In two contrasting reviews by Crawford and Suy, complete resolution of the periaortic inflammatory mantle was reported after repair of the inflammatory aneurysm by graft insertion. They concluded that there is no role for ureterolysis in repair of these aneurysms.^{3,39} In Sterpetti's study, there were no reports of late ureteral obstruction with a mean follow-up interval of 6 years.⁷ Pennell et al. had similar results of no late ureteral obstruction in 126 patients who underwent repair of an inflammatory abdominal aortic aneurysm.² Therefore, these authors advised against ureterolysis as an operative technique.

In contrast, a recent study by Stella et al.⁹ described the postoperative course of patients who underwent repair of inflammatory AAAs without ureterolysis. In 53% of these patients, preoperative CT scan showed the ureters to be incorporated in the periaortic inflammatory mass. Postoperative abdominal CT scans showed that complete regression of the periaortic inflammatory mantle occurred in only 47% of patients.⁹ Partial regression occurred in 21% and no change in 31.7%. Of interest however, is that no patient had progression of the inflammatory process. Specifically, 7 of the 10 patients with ureteral entrapment showed complete regression of inflammatory mass and spontaneous release of the ureters, and 2 of the 10 showed partial regression. The one patient in whom no regression occurred after aneurysm repair remained clinically asymptomatic after 24 months.

In our recent follow-up of 29 patients with inflammatory AAAs, we discovered findings similar to Stella's observations.^{9,19} The inflammatory process persisted in 47% of the patients at a mean follow-up of 18 months. The ureters remained entrapped in 32% of the patients and 47% had signs of unilateral or bilateral renal atrophy by CT scan. Chronic dialysis became necessary in one

(3%) patient at a mean follow-up of 18 months. Because the prevailing thought was that the perianeurysmal inflammatory response resolved after tube graft placement and aneurysms repair, ureterolysis was performed in only one (3%) patient in this study. Regardless of the outcome of the entrapped ureters, clinical symptoms (abdominal pain, malaise, and weight loss) reversed in 93% of the patients.¹⁹

ETIOLOGY AND PATHOGENESIS

Controversy exists regarding the cause and pathogenesis of inflammatory AAAs. Walker et al. proposed that they were distinct clinical and pathological entities different from noninflammatory aneurysms, and this view of inflammatory AAAs has prevailed.¹² Early publications in the urologic literature suggested that the periaortic fibrosis was a reaction to retroperitoneal blood leaking from tiny subclinical perforations of the noninflammatory AAA.⁴⁰⁻⁴² This theory has been refuted by studies that fail to show hemosiderin-laden macrophages in the perianeurysmal inflammatory mantle.^{40,43}

Other surgeons believe that the atherosclerotic aneurysm formation is the preceding phenomena and that the inflammatory response is dependent on the aneurysm itself and contact between blood and aortic wall.³ Crawford's study supported this theory by showing that after aneurysm repair the periaortic inflammatory response seemed to resolve in 100% of patients. Using CT scan follow-up, more recent studies found that complete or partial regression of the periaortic inflammatory response occurred in only 53% to 68% of patients after aneurysm repair.^{9,19} Sterpetti et al. also concluded that aneurysm formation precedes the periaortic inflammatory reaction.⁷ They recognized hyperplastic periaortic lymph nodes in many patients and suggested that compression of the lymphatic vessels by the enlarging aneurysm results in stasis, edema, and a secondary fibrotic reaction.

In 1981, Rose and Dent proposed a novel hypothesis on the cause of the inflammatory AAA.⁴⁴ Through histologic grading of 51 consecutively repaired AAAs, they showed that an inflammatory process was present in the aneurysm wall in all specimens to varying degrees. Mild chronic inflammation and fibrosis was present in 72% of the aneurysms and moderate changes in 16% of aneurysms. Severe inflammation and fibrosis associated with aneurysmal wall thickening was present in 12% of all aneurysms. They noted that no sharp distinction existed between the usual atherosclerotic aneurysm and the inflammatory aneurysm. For the first time, they proposed that the inflammatory aneurysm was the extreme end of an inflammatory process responsible for both the inflammatory and noninflammatory AAA. In contrast to Walker's original definition, they concluded that the inflammatory aneurysm was not a distinct clinical and pathologic entity but an "in-

flammatory variant" of the well-known atherosclerotic AAA.⁴⁴

Pennell et al. showed that a chronic inflammatory infiltrate occupying the adventitia existed in both atherosclerotic and inflammatory AAAs. They emphasized that the only difference is in the "intensity and extent of the inflammatory process, suggesting that they are the same disease process differing only in the progression of the inflammation".² In a similar manner, Sterpetti described "a gradual passage, in terms of inflammatory response, from ordinary atherosclerotic to inflammatory response".⁷ A related finding by Latifi et al. described the development of an inflammatory AAA from a noninflammatory AAA as observed by abdominal CT scan during the course of 7 months.⁴⁵

Emerging data support this theory and suggest a primary inflammatory response to an unknown antigen presented to the aortic wall. This response is characterized by aortic-wall infiltrating macrophages, T lymphocytes, and B lymphocytes that activate proteolytic activity through the production of cytokines.⁴⁶⁻⁴⁹ This proteolytic activity leads to increased turnover in the matrix proteins, elastin, and collagen.⁵⁰ Subsequent loss of aortic wall integrity and tensile strength occur as an aneurysm forms.⁵¹⁻⁵⁷ This inflammatory process is accentuated in certain persons with environmental risks (*e.g.*, smoking) or a genetic predisposition. The extreme end of the inflammatory spectrum is reached and results in an inflammatory AAA at a relatively younger age.

Other recent studies have investigated the morphology of extracellular matrix modifications, particularly elastin in both inflammatory and noninflammatory AAAs.^{46,58} Using scanning and immunoelectromicroscopy as well as immunohistochemical techniques, these studies have shown extensive extracellular matrix remodeling. These changes included varying degrees of elastin depletion resulting from an inflammatory infiltrate. These changes secondary to the inflammatory infiltrate were observed in both inflammatory and noninflammatory aneurysms.

In searching for a unified hypothesis for the formation of inflammatory and noninflammatory AAAs, we have been impressed with their similarity to another arterial disease. This disease is giant cell arteritis (GCA) which affects the medium and large arteries of the body.⁵⁹⁻⁶¹ Immunohistochemical studies in patients with GCA show tissue-infiltrating T lymphocytes and macrophages directing an inflammatory process in the media and adventitia.⁶²⁻⁶⁴ Similar to inflammatory and noninflammatory aneurysm development, the inflammatory process in the arteries of GCA disrupts the matrix proteins and the internal elastic lamina. Weyand et al. showed that the inflammatory process within the vessels of GCA is directed by the T lymphocyte as well as by macrophage activation through production of interleukin-2 and interferon- γ .^{65,66} Furthermore, patients with GCA present clinically with

fatigue, malaise, and an elevated erythrocyte sedimentation rate similar to patients with inflammatory AAAs.^{59,67}

Through HLA typing of patients with GCA, Weyand et al. also provided direct evidence of a genetic predisposition to this disease. They showed that GCA is an HLA-associated disease. By the sequencing of HLA-DR genes in patients with GCA, they identified a sequence stretch within the second hypervariable region of the HLA-DRB1 gene as a key genetic element in GCA patients.^{59,68-72} Interestingly, this sequence motif is mapped to the floor of the antigen-binding site of the folded HLA-DR molecule suggesting that selection and binding of antigenic peptides is critically involved in the disease process.

These findings raise further questions about the cause of inflammatory aneurysms. In light of the familial tendency to develop both inflammatory and noninflammatory AAAs, locating a genetic locus shared by aneurysm patients is a logical approach to our basic research. Clearly, the HLA-DR genes should be considered candidate genes. As in patients with GCA, polymorphic structures within the HLA molecule may predispose individuals to develop inflammatory AAAs. Identification of HLA-encoded genetic factors rendering individuals susceptible to the destructive inflammatory response in the wall of the aorta would open the possibility to search for disease-relevant antigens.

Another possible causal factor is an infection (*e.g.*, bacterial or syphilitic). However, bacterial cultures of the aneurysm wall consistently have been negative. Serologic tests for syphilis have also been negative in the majority of patients with inflammatory AAAs.^{1,3,7,44} Could viral infection play a role in AAA development? Recently, Tanaka et al. published evidence that the human herpes virus may play a role as an antigen in the pathogenesis of aortic diseases.^{71,72} Using DNA polymerase chain reaction, they showed that either the herpes simplex virus or cytomegalovirus was present more frequently in the wall of aneurysms than in normal aortic wall. In addition, these viruses were more prevalent in inflammatory than noninflammatory AAAs. They hypothesized that the replicating infections of the cytomegalovirus may cause the formation of inflammatory aneurysms.^{71,72}

Whereas this evidence is suggestive and thought-provoking, the exact cause of both inflammatory and noninflammatory AAAs is likely multifactorial (Fig. 7). A combination of environmental, endothelial, and genetic factors act on the vessel wall and cause aneurysm formation. These same factors may be responsible, in certain persons, for the development of the inflammatory AAA. Further studies to better characterize these factors and the molecular and cellular mechanisms at play in the pathogenesis of inflammatory AAAs are required.

CONCLUSION

Remarkable progress has been made in the diagnosis and management of abdominal aortic aneurysms since the

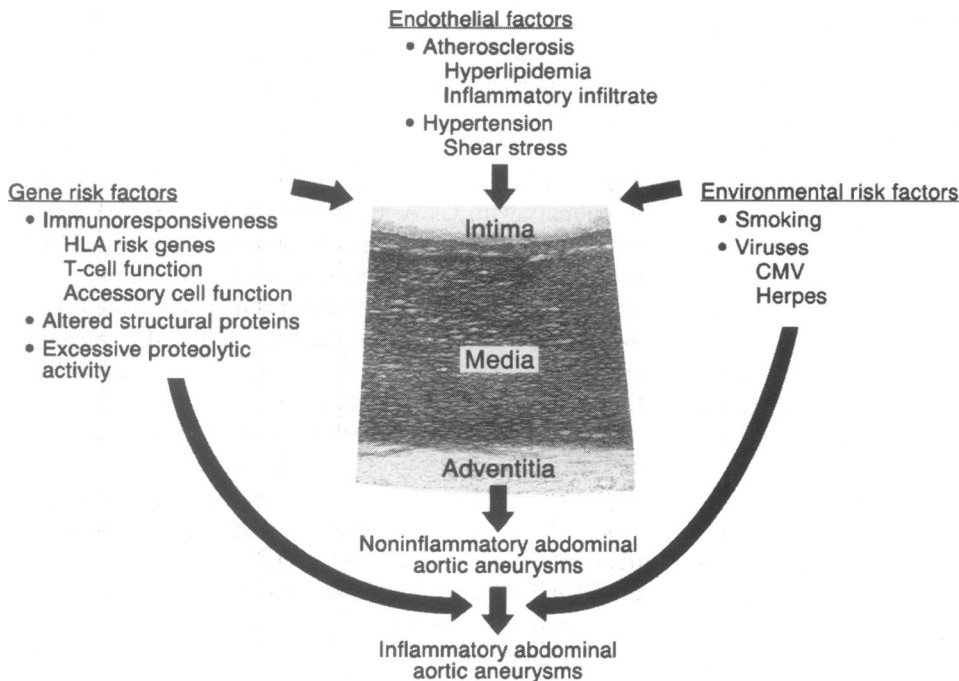


Figure 7. A schematic representing the multifactorial pathogenesis of aneurysm development. The three categories of risk factors, genetic, endothelial, and environmental, may also play a role in the progression from the noninflammatory aneurysm to the inflammatory abdominal aortic aneurysm.

first repair by Dubost in 1951. However, one of the clinical challenges remains the so-called inflammatory aneurysm. Recent clinical findings reveal stronger links to current smoking and familial tendencies. Smoking and or viruses may represent environmental risk factors that accentuate an inflammatory response, while the familial tendency may represent a genetic defect in immunoresponsiveness, tissue repair, or structural proteins. The histologic similarities of inflammatory AAAs and GCA are striking. Currently, basic research on aneurysm development is focusing on lymphocyte function, cytokines, and the antigens that drive this inflammatory response (e.g., viruses). Identification of this instigator may eventually lead to adjunctive pharmacologic interventions for the spectrum of inflammatory and noninflammatory abdominal aortic aneurysms.

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